UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/618,540	07/09/2003	Sai Kiang Lim	4810-66314	8220

7590 06/27/2005

One World Trade Center
Suite 1600
121 S.W. Salmon Street
Portland, OR 97204

EXAMINER	
BARNHART, LORA ELIZABETH	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 06/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/618,540	LIM, SAI KIANG	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *5-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 July 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/12/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

$0.00

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-5, in the reply filed on 6/13/05 is acknowledged. The traversal is on the ground(s) that claim 17 comprises the matter of claim 3 as an "essential feature" of claim 17. This is not found persuasive because the composition of claim 17 necessarily requires that the preparation of claim 3 be "modified" such that the cells of said preparation carry a "therapeutic" gene. This requirement imposes issues of anticipation and obviousness not present in any of claims 1-5, in addition to presenting issues of utility, enablement, and indefiniteness not present in any of claims 1-5.

Applicants further request that claims 14 and 15 be rejoined to Group II because they have been amended to depend therefrom. This is not found persuasive because the amendments to claims 14 and 15 are confusing and do not clearly place said claims within Group II. As pointed out in the requirement for restriction, Group II is drawn to a method of **preparing** a mammalian hemangioblast line, while Groups IV and V are drawn to methods of **using** the product of said method. As dictated by *in re Brouwer* and *in re Ochiai*, methods of use will be rejoined only with an allowable product at the time of allowance. Applicants' request that Groups IV and IV be rejoined to Group II is denied for at least these reasons.

Applicant further asserts, "the subject matter of all of the claims is sufficiently related" that a search for the subject matter of Group I would necessarily encompass the matter of Groups II-VII. This argument is unpersuasive for two reasons. First of all,

this application was filed under 35 U.S.C. § 111, not 35 U.S.C. § 371, so applying the lack of unity standard (as seemingly suggested by applicants) is improper and unnecessary. In addition, applicants assert that since most patents require a search of more than one class and subclass, presumably without burden, searching each and every one of claims 1-17 would not burden the examiner. In fact, burden consists not only of specific searching of classes and subclasses, but also of searching multiple databases for foreign references and literature searches. Burden also resides in the examination of independent claim sets for clarity, enablement and double patenting issues.

Applicant has further traversed the requirement for an election of species, again maintaining that searching all six claimed cell types in all mammals would not be burdensome, since all of the cells are classified in 435/325. As noted above, burden consists not only of specific searching of classes and subclasses, but also of searching multiple databases for foreign references and literature searches. Burden also resides in the examination of independent claim sets for clarity, enablement and double patenting issues.

The requirement is still deemed proper and is therefore made FINAL. Claims 6-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claim 5 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim.

Examination will continue at this point on claims 1-4 ONLY, to the extent that they read on human hemangioblast cells.

Drawings

The drawings are objected to because the photographs of cells and gels are dark and/or illegible. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to

identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-4 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-3 of copending Application No. 10/521071, which at this time is not available to the examiner. This rejection is based on the claims in the corresponding WIPO document (PCT/SG2003/000169) of which the co-pending application is the 35 U.S.C. § 371 filing.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement and written description requirements. The claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims also contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventor(s), at the time the application was filed, had possession of the claimed invention.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

As applicant has admitted (page 2, line 32, through page 3, line 5), the isolation of hemangioblasts has not been reported in the literature and is, in fact, a topic of heated debate within the art. In a literature review in a peer-edited textbook, Keller (2001, IDS reference A22) characterizes the hemangioblast cell as a "hypothesis" (page 329) and teaches that despite a body of evidence supporting its existence, "a cell with the characteristics of the hemangioblast has not yet been isolated from developing embryos" (page 329-330). The notion of a "hemangioblast", *i.e.* a cell that is the common precursor to both the hematopoietic and endothelial lineages, is supported by the fact that said lineages express common markers (Choi et al., 1998; IDS reference A10). Even after the time of the instant invention, though, Dieterlen-Lièvre et al. characterize that existence of hemangioblasts as "hypothetical" (2004, *Mechanisms of Development* 121: 1117-1128; reference U; see page 1121, column 1). Dieterlen-Lièvre

et al. further teach that hemangioblasts have been difficult to observe or to isolate from mammals (page 1126, column 1). For at least these reasons, the examiner has interpreted "hemangioblast" to mean "precursor cell that gives rise to both hematopoietic and endothelial lineages".

Kennedy et al. (1997, IDS reference A25) describe the blast colony-forming cell (BL-CFC), which is derived from differentiated ES cells and can form colonies that express the hematopoietic lineage markers Flk-1, CD34, and Tal-1/SCL (page 491, column 2). Choi et al. (reference A10) further teach that under certain conditions, BL-CFC become adherent and express the endothelial lineage marker CD31, as well as the Flk-1 marker that is expressed by cells in both the hematopoietic and endothelial lineages (page 727, column 2, through page 728, column 1). Choi et al. conclude that the BL-CFC is a *bona fide* precursor for both hematopoietic and endothelial cell lineages (page 730, column 1), but skilled artisans have not reached consensus that this is the case. See, for example, Dieterlen-Lièvre et al. (published 8 years after Choi et al. and at least one year after the instant invention), as discussed above. Keller, the principal investigator for both the Choi et al. and Kennedy et al. studies, himself admitted in 2001 (years after the publication of Choi et al. and Kennedy et al.) that the existence of such a precursor as a single, isolatable cell type is in dispute among skilled artisans (IDS reference A22; see pages 335, 336, and 339).

While there is evidence that hematopoietic cells and endothelial cells arise from a single precursor, the results of at least one study indicate that this is not the case. Kinder et al. (1999, *Development* 126: 4961-4701; reference V) found that in yolk sac

mesoderm, hematopoietic precursors and endothelial precursors arise at different times, not simultaneously (page 4699, column 2), a result which does not support the notion of a single precursor for both of these lineages.

Even if a single precursor for the hematopoietic and endothelial lineages does exist (which the examiner certainly does not concede), a person of ordinary skill in the art would not have a reasonable expectation that the cells instantly described and claimed by applicants are said precursor. The state of the art dictates that hematopoietic precursors and endothelial precursors each express a specific set of identifying markers. For example, Kennedy et al. (reference A25) teach that hematopoietic precursors express at least Flk-1 and CD34 (page 491, column 2), while Choi et al. (reference A10) teach that endothelial precursors express at least Flk-1 and CD31 (page 717, column 2). This characterization is generally agreed upon by skilled artisans; for example, Ema et al. (2003, *Trends in Cardiovascular Medicine* 13: 254-250; reference W) teach that endothelial and hematopoietic progenitors both express at least Flk-1 and Tie-2 (page 254, column 3). If hematopoietic progenitors express Flk-1, Tie-2, and CD34, and endothelial progenitors express Flk-1, Tie-2, and CD31, the logical conclusion (and, indeed, the conclusion reached by Choi et al.) for the expression profile of a cell that is the precursor to both is that it would express at least all of these markers. The instant specification, on the other hand, indicates that the alleged precursors of hematopoietic and endothelial cell lineages express none of these markers (page 32, lines 3-10). Quite simply, absent ample substantive evidence to the

contrary, the skilled artisan would not consider it obvious that a cell population expressing no markers of either lineage would give rise to either lineage.

In addition, the instant specification describes the isolation of cells that are precursors to both the hematopoietic and endothelial lineages from adult bone marrow sources. Because the claims have been elected to read on human cells, Examples 3-5 (pages 36-38) must be carefully evaluated. If the existence of the hemangioblast *per se* is in dispute, the existence of such cells derived from adult tissue must be viewed with even greater skepticism. Indeed, Bailey et al. (2003, *Experimental Hematology* 31: 987-993; reference X) are among the first to speculate as to the presence in adult bone marrow of cells that give rise to both hematopoietic and endothelial lineages (page 990, column 2, through page 991, column 2). Because the "hemangioblast" was described by Murray in 1932 as an embryonic structure, and has been sought by the laboratory of Keller as recently as 2001 as a derivative of embryonic stem cells, the presence of a so-called "adult hemangioblast" must be considered even more unproven than that of the original embryonically-derived "hemangioblast". Absent a significant evidentiary showing, the skilled artisan would simply not have a reasonable expectation that human bone marrow would comprise precursor cells that give rise to both hematopoietic and endothelial lineages.

In short, the specification as filed, in light of the unpredictable nature of the art, fails to provide ample description such that a person of ordinary skill in the art would have a reasonable expectation of obtaining precursors that give rise to both hematopoietic and endothelial lineages in the manner described in Example 3. The

specification also fails to provide sufficient guidance such that the skilled artisan would have a reasonable expectation (in light of the prior art and post-filing art) of obtaining and isolating said precursors as claimed.

Claims 1-4 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The invention appears to employ novel biological materials, specifically HuSH cells (Example 3, page 37 line 29). Since the biological materials are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the biological materials are not so obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological materials.

The specification does not disclose a repeatable process to obtain the biological materials, and it is not apparent if the biological materials are readily available to the public. Applicant does not seem to have deposited the biological materials, and there is no indication in the specification as to public availability. If the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific biological materials have been deposited under the Budapest Treaty and that the biological materials will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit must be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R. §1.807) and

(e) the deposit will be replaced if it should ever become inviable.

Applicant's attention is directed to M.P.E.P. § 2400 in general, and specifically to § 2411.05, as well as to 37 C.F.R. § 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination." The specification should be amended to include this information; however, Applicant is cautioned to avoid entry of new matter into the specification by adding any other information.

Finally, Applicant is advised that the address for the ATCC has recently changed, and that the new address should appear in the specification. The new address is:

American Type Culture Collection
10801 University Boulevard
Manassas, VA 20110-2209

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites, "a purified preparation of mammalian **hemangioblast** cells", which is confusing. As noted above in the rejections under 35 U.S.C. 112, first paragraph, the term "hemangioblast" is controversial within the art. Murray (1932, IDS reference A36) specifically "restrict[s] the term 'hemangioblast' to the mass [of cells from which develop the endothelial vessels containing plasma and the blood islands] and use for the component cells the infrequently needed term 'hemangioblast cell'" (page 498, paragraph 2). Keller (2001, IDS reference A22) teaches that recently, the term has been taken to refer to "a single cell, the hypothetical precursor of the hematopoietic and endothelial lineages" (page 329, paragraph 1). The term's meaning is clearly elastic over time, and by Keller's definition, it does not refer to any specific characterized cell, but rather to a theoretical precursor whose presence is disputed in the art. The claim should be rewritten such that it claims the exemplified composition and does not refer to a purported function or developmental property thereof. Because claims 2-4 depend from indefinite claim 1 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim 2 recites "PECAM-1 (or CD31)", which is confusing. It is not clear whether the information in parentheses is required for the claim, whether it is intended to broaden the claim, or whether it is intended to narrow the claim. Clarification is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by a fraction of human bone marrow, taken in light of Rafii et al. (2003, *Nature Medicine* 9: 702-712; reference U2). The claims are drawn to a composition comprising cells that give rise to both hematopoietic and endothelial lineages, said composition having numerous properties as recited in claim 1. In some dependent claims, the cells do not react with various markers. In some dependent claims, the cells are human.

Bone marrow naturally comprises both endothelial precursor cells (EPCs) and hematopoietic stem cells (HSCs), as is reviewed by Rafii et al. (see, for example, Table 1). The preparation therefore differentiates to both hematopoietic and endothelial cell lineages.

Claims 1-4 are also rejected under 35 U.S.C. 102(b) as being anticipated by Reubinoff et al. (2000, *Nature Biotechnology* 18: 399-404; reference V2). The claims are drawn to a composition as described above.

Reubinoff et al. teach the isolation of embryonic stem (ES) cells from human blastocysts (page 399, column 2). Reubinoff et al. further teach that human ES cells can differentiate to mesoderm (see, for example, the abstract); both bone marrow and endothelial cells arise from mesoderm.

Claims 1 and 3 are also rejected under 35 U.S.C. 102(b) as being anticipated by Choi et al. (IDS reference A10). The claims are drawn to a composition as described above.

As already discussed, Choi et al. teach a composition of blast-colony forming cells having both hematopoietic and endothelial potential (pages 727-728).

The Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether or not applicants' cell composition differs, and if so to what extent, from the cell compositions discussed in the prior art. Accordingly, it has been established that the prior art cells, which have the ability to differentiate to both hematopoietic and endothelial cell lineages, demonstrate a reasonable probability that they are either identical or sufficiently similar to the claimed cells that whatever differences exist are not patentably significant. Therefore, the burden of establishing novelty or unobviousness by objective evidence is shifted to applicants.

Merely because a characteristic of a new composition is not disclosed in a reference does not make the known composition (in this case, bone marrow or ES cells) patentable. The new composition possesses inherent characteristics which might not be displayed in the tests used the reference. Clear evidence that the composition of the cited prior art do not possess a critical characteristic (for example, that the ES cells of

Reubinoff et al. or the BL-CFCs of Choi et al. do not react with the recited markers and that they possess the recited characteristics) that is possessed by the claimed composition, would advance prosecution and might permit allowance of claims to applicants' composition.

No claims are allowed. No claims are free of the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Friday, 8:00am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lora E Barnhart

leb

IRENE MARX
PRIMARY EXAMINER